ISSN 1936-878X/09/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2008.10.005

EDITORIAL COMMENT

Role of Echocardiography in Predicting Onset of Heart Failure in Patients With Stable Coronary Artery Disease

Is the Whole Greater Than the Sum of its Parts?*

Miguel A. Quinones, MD, FACC

Houston, Texas

Despite great improvements in the prevention and treatment of coronary artery disease (CAD), the prevalence of heart failure (HF) continues to rise, and CAD remains a common etiology for this disorder (1,2). This apparent paradox is partially explained by the increasing prevalence of risk factors for HF, including the number of patients surviving myocardial infarction (MI) with reduced left ventricular (LV) ejection fraction (EF). The American College of Cardiology/American Heart Association (ACC/AHA) 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult classified HF into 4 stages, the first 2 representing subclinical stages that pre-dispose patients to clinical HF (2). In stage A, patients have major risk factors such as hypertension, CAD, obesity, or diabetes, without known structural heart disease; patients in stage B have evidence of structural heart disease (previous MI, concentric left ventricular hypertrophy, LV remodeling, or low EF) that further increases their risk for clinical HF. This classification allows physicians to introduce preventive measures to reduce the incidence of HF in populations at risk. This is of great importance because the first hospitalization for HF worsens survival for most patients, regardless of resting EF (3–5). Given that recognition of stage B HF is facilitated by echocardiography, there has been great interest in exploring the prognostic value of echocardiographic findings in populations at risk for HF.

See page 11

In this issue of *iJACC*, Stevens et al. (6) explored the hypothesis that findings derived from a resting transthoracic echocardiogram in patients with CAD can be combined to develop a risk-stratification index that predicts HF hospitalization. They studied 1,024 ambulatory subjects participating in the Heart and Soul Study, all of whom had clinical characteristics that placed them in stage A or B heart failure (known CAD, previous MI [>6 months], hypertension). More than 80% of the participants had never experienced a hospitalization for HF, and the majority (92.7%) had an EF >45% (mean EF: 62 ± 10%; range: 13% to 83%).

Using the Cox proportional hazard model, the authors assessed the association of 15 transthoracic echocardiogram measurements with subsequent HF hospitalization. Although most of the variables were identified as predictors of HF hospitalization by univariate analysis, only 5 were independent predictors: mitral regurgitation (MR), left atrial volume index (LAVI), LV mass index, the integral of the velocity in the LV outflow tract by pulsed-wave Doppler (VTI_{LVOT}), and diastolic dysfunction (i.e., pseudonormal or restrictive mitral inflow pattern indicative of elevated filling pressures). The authors applied a point-scoring system to the 5 variables to develop a HF risk index (RI) with a scale ranging from 0 to 8 (1 point each given for ≥ mild MR, LAVI >29 ml/m^2, VTI_{LVOT} <22 cm; 2 points for diastolic dysfunction; and 3 points for LV mass index >90 g/m^2). During an average follow-up of 4.4 years, HF hospitalizations were observed in 4% of participants with an RI of 0 to 2 compared with 10% with an RI of 3 to 4 ($p = 0.003$); 24% with an RI of 5 to 6 ($p < 0.0001$); and 48% with an RI of 7 to 8 ($p < 0.0001$). The

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

From the Department of Cardiology, Methodist Hospital and the Methodist DeBakey Heart and Vascular Center, Houston, Texas.

JACC: CARDIOVASCULAR IMAGING, VOL. 2, NO. 1, 2009
JANUARY 2009:21–3

association between the RI and HF hospitalization remained significant even after adjusting for several comorbidities. Results were similar, but with lower risks in the 831 participants without a previous history of HF.

Four of the 5 components of the HFRI have been identified previously as predictors of outcome in patients with CAD and/or LV dysfunction. In MI survivors, the presence of functional/ischemic MR, even if mild, is associated with higher mortality and worsening of HF (7). Left atrium (LA) enlargement and diastolic dysfunction have been shown to predict worse outcomes in patients with CAD, hypertension, and/or LV dysfunction (8–15). Left ventricular dilation (i.e., eccentric hypertrophy) and concentric hypertrophy are both associated with a greater prevalence of cardiovascular events and death, and both are captured by measuring LV mass (10,16–18). In fact, in multiple studies, LV mass consistently appears as a strong independent predictor of outcome. In a cohort of 1,172 patients enrolled in the SOLVD (Studies Of Left Ventricular Dysfunction) trials (n = 577) and registry (n = 595), LV mass, LA size, and EF were independent predictors of 1-year mortality and the rate of cardiovascular hospitalizations (10). Left ventricular mass was a strong predictor, and at lower ranges, had a protective effect irrespective of EF. The fact that close to 98% of the participants in this study had preserved EF explains why this measurement lost power as an independent predictor of HF hospitalization.

Although each of the 5 echocardiographic parameters in this study predicted outcome, when combined into an HFRI, the prediction of risk was superior to that provided by any single parameter. This is a good example of "the whole is greater than the sum of its parts." There are several examples in medicine in which individual parameters are combined into a risk stratification score; perhaps the most commonly known in cardiology is the Framingham Risk Score, which combines sex, age, blood pressure, cholesterol levels, diabetes, and smoking to predict a 10-year risk of developing CAD (19). Therefore, this concept makes clinical sense and has a strong statistical basis.

Although the components of the HFRI are commonly used by clinical echocardiographers, measurement techniques vary between laboratories, and this could influence the cut-off values used to determine the HFRI. The authors measured LA volume with the biplane method of disc, but other laboratories use the area-length method; both are endorsed by the American Society of Echocardiography (20). However, normal ranges vary slightly between these methods. Similarly, LV mass was measured with the truncated ellipsoid equation, but other laboratories use the American Society of Echocardiography modification of the cube formula, which has slightly different normal ranges. The authors defined pseudonormal diastolic dysfunction as a peak mitral early diastolic to atrial contraction velocity (E/A) ratio between 0.76 and 1.4, with diastolic-dominant pulmonary vein flow, and a restrictive pattern as an E/A $\geq$1.5, with diastolic dominant pulmonary vein flow. These patterns are markers for elevated LV filling pressures and were initially described in patients with depressed LV function using the E/A ratio and deceleration time (9). However, they are known to lose accuracy in patients with preserved EF (21). Consequently, most laboratories currently use the ratio of transmitral E-velocity to early diastolic annular velocity by tissue Doppler (E/E') to better define these patterns, particularly in patients with normal EF; an E/E' $\geq$15 detects a mean left atrial pressure >15 mm Hg and is a marker of advanced diastolic dysfunction (15,22). This ratio has also been shown to predict HF events in populations at risk (14,15). Using E/E' to define diastolic dysfunction could have important influence on the HFRI, perhaps by improving its predictive accuracy. It may be worthwhile to investigate this hypothesis prospectively.

Ultimately, the value of any risk stratification method is to identify patients who benefit from more aggressive preventive measures. All of the study participants were in stage A or B heart failure and would benefit from aggressive management of their risk factors (2). Consequently, it is not clear how much more is gained by restratifying them with an echocardiographic HFRI. Perhaps patients in stage A with an HFRI >5 would benefit from receiving therapy recommended for stages B or C, particularly if they have evidence of diastolic dysfunction (i.e., elevated filling pressures). The only answer to this question would come from a randomized clinical trial in which 1 group is treated based on an HFRI, while the other is managed according to the ACC/AHA guidelines. Until then, we should adhere to the ACC/AHA recommendations. Nevertheless, the echocardiographic HFRI represents an important step in simplifying data from a routine transthoracic echocardiogram and using it to enhance our assessment of risk for heart failure hospitalization in selected patients.

Reprint requests and correspondence: Dr. Miguel A. Quinones, Department of Cardiology, Methodist Hospital, Cardiology, 6550 Fannin, Suite 1901, Houston, Texas 77030. *E-mail: maquinones@tmhs.org.*

REFERENCES

1. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics—2008 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117: e25–146
2. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2005;46:1116–43.
3. Yancy CW, Lopatin M, Stevenson LW, et al. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 2006;47: 76–84.
4. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260–9.
5. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006; 355:251–9.
6. Stevens SM, Farzaneh-Far R, Na B, Whooley MA, Schiller NB. Development of an echocardiographic risk-stratification index to predict heart failure in patients with stable coronary artery disease: the Heart and Soul study. J Am Coll Cardiol Img 2009; 2:11–20.
7. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001;103:1759–64.
8. Moller JE, Hillis GS, Oh JK, et al. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. Circulation 2003;107: 2207–12.
9. Xie GY, Berk MR, Smith MD, Gurley JC, DeMaria AN. Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure. J Am Coll Cardiol 1994;24: 132–9.
10. Quiñones MA, Greenberg BH, Kopelen HA, et al., for the SOLVD Investigators. Echocardiographic predictors of clinical outcome in patients with left ventricular dysfunction enrolled in the SOLVD registry and trials: significance of left ventricular hypertrophy. J Am Coll Cardiol 2000; 35:1237–44.
11. Ren X, Ristow B, Na B, Ali S, Schiller NB, Whooley MA. Prevalence and prognosis of asymptomatic left ventricular diastolic dysfunction in ambulatory patients with coronary heart disease. Am J Cardiol 2007;99: 1643–7.
12. Takemoto Y, Barnes ME, Seward JB, et al. Usefulness of left atrial volume in predicting first congestive heart failure in patients > or = 65 years of age with well-preserved left ventricular systolic function. Am J Cardiol 2005; 96:832–6.
13. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin JM, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol 2001;37:1042–8.
14. Yu CM, Sanderson JE, Marwick TH, Oh JK. Tissue Doppler imaging a new prognosticator for cardiovascular diseases. J Am Coll Cardiol 2007;49: 1903–14.
15. Brucks S, Little WC, Chao T, et al. Contribution of left ventricular diastolic dysfunction to heart failure regardless of ejection fraction. Am J Cardiol 2005;95:603–6.
16. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561–6.
17. Ghali JK, Liao Y, Simmons B, Castaner A, Cao G, Cooper RS. The prognostic role of left ventricular hypertrophy in patients with or without coronary artery disease. Ann Intern Med 1992;117:831–6.
18. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Levy D. Left ventricular dilatation and the risk of congestive heart failure in people without myocardial infarction. N Engl J Med 1997;336:1350–5.
19. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47.
20. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
21. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788–94.
22. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527–35.

Key Words: echocardiography ■ heart failure ■ coronary artery disease.